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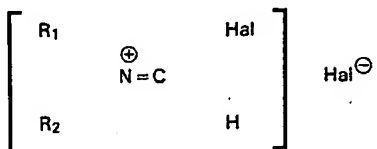
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54 Preparing clindamycin and analogues thereof.

57 A process for preparing 7-halo-7-deoxylincomycin or an analogue thereof, which comprises

(a) reacting a starting compound selected from lincomycin and analogues thereof, with an amide halide having the formula



wherein each Hal is bromine or chlorine, and either R<sub>1</sub> and R<sub>2</sub> are independently selected from aryl and C<sub>1-8</sub> alkyl or NR<sub>1</sub>R<sub>2</sub> is morpholino or a heterocyclic ring containing 4 to 8 ring atoms selected from carbon and nitrogen, to form an adduct;

(b) heating the adduct, to form a 7-halo-7-deoxy adduct; and

(c) hydrolysing the 7-halo-7-deoxy adduct with an aqueous base.

PREPARING CLINDAMYCIN AND ANALOGUES THEREOF

The present invention relates to a process for preparing 7-halo-7-deoxylincomycins (including clindamycin) from lincomycin and analogues thereof. Clindamycin is a well-known antibiotic.

US-A-3435025, US-A-3496163 and US-A-3509127 disclose such a process, in which the 7-hydroxyl group of the starting compound, i.e. lincomycin or an analogue thereof, is replaced with a halogen group, by reaction with a Rydon reagent and heating the resulting product. The use of thionyl chloride for such a process is described in US-A-3496163, US-A-3509127 and US-A-3574186. A process for preparing 7-halo-7-deoxylincomycin by the use of a sulfite-protected lincomycin and Rydon reagents is described in US-A-3714141.

The use of a Vilsmeier reagent to substitute a halo atom for a hydroxyl group is described by Eilingsfeld et al, Angew. Chem. 72 (1960) 836, and Chem. Ber. 96 (1963) 2671. Evans et al, JOC 33 (1968) 1074, disclose that, while a Vilsmeier reagent prepared from methanesulfonyl chloride and dimethylformamide was successfully used to replace a primary hydroxyl group, it was not successful in attempts to replace a secondary hydroxyl group.

The structure of the adduct formed between dimethylformamide and thionyl chloride has been investigated by Ferre et al, Tet. Lett. (1969) 2161. Conditions for converting the adduct to the corresponding amide chloride have been described by Kikagawa et al, Chem. Pharm. Bull. 19 (1971) 2629. Bosshard et al, Helv. Chim. Acta. 42 (1959) 16153, disclose the use of dimethylformamide as a catalyst in the conversion of carboxylic acids to acid chlorides.

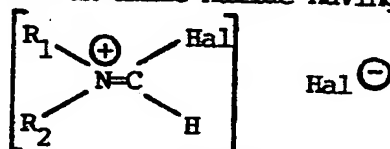
Hepburn et al, J. Chem. Soc. Perkin I (1976) 754, and Chem. & Ind. (1974) 664, describe the use of amide chlorides obtained from Vilsmeier reagents, to replace hydroxyl groups by chlorine or bromine groups. The hydroxyl-containing compounds were relatively simple alcohols.

The use of a mixture of mesyl chloride and dimethylformamide to replace primary groups of hexopyranosides by chlorine, is described by Edwards et al, Tet. Lett. (1973) 2369. The halogenation of nucleosides by amide chlorides is described by Dobs et al, Tet. Lett. (1969) 165.

It is unclear, from the prior art, as to whether the Vilsmeier reagent is more generally effective than the amide chloride, the result of removing sulphur dioxide.

According to the present invention, a process for preparing  
5 7-halo-7-deoxylincomycin or an analogue thereof comprises

(a) reacting a starting compound selected from lincomycin and analogues thereof, with an amide halide having the formula



wherein each Hal is bromine or chlorine, and either  $R_1$  and  $R_2$  are  
10 independently selected from aryl and  $C_{1-8}$  alkyl or  $NR_1R_2$  is morpholino or a heterocyclic ring containing 4 to 8 ring atoms selected from carbon and nitrogen, to form an adduct;

(b) heating the adduct, to form a 7-halo-7-deoxy adduct; and

(c) hydrolysing the 7-halo-7-deoxy adduct with an aqueous  
15 base.

One advantage of the novel process is that the use of an amide halide, rather than a Vilsmeier reagent, gives increased yields and reduced amounts of by-products. Another advantage is that hydrated lincomycin can be used without detrimentally affecting the yield or  
20 quality of the product.

The starting compound is preferably lincomycin. Examples of analogues which can be used are methylthiolincosaminide, lincomycin-3,4-acetonide, 3,4-cumylidenelincomycin, 3,4-(p-t-butylbenzylidene)lincomycin and 3,4-benzylidenelincomycin. The  
25 product of the process is preferably clindamycin. Examples of analogues, prepared using the starting compounds exemplified immediately above, are 7-chloromethylthiolincosaminide, clindamycin-3,4-acetonide, 3,4-cumylideneclindamycin, 3,4-(p-t-butylbenzylidene)clindamycin and 3,4-benzylideneclindamycin.

30 In step (a), lincomycin or an analogue thereof, either in its free form or as an anhydrous or hydrated salt, is reacted with an amide halide. Amide chlorides, especially those prepared from N-formylpiperidine and dimethylformamide, are preferred. The reaction is conducted in the presence of a solvent at -10

to 40°C for a reaction time of about several minutes to several hours. Preferred reaction temperatures and times are about 0° to 5°C and 10 to 30 minutes, respectively. Solvents that can be used include chlorinated hydrocarbons such as methylene chloride, 1,2-dichloroethane; various chlorinated aromatics (i.e. chlorobenzene, dichlorobenzene, etc.); acetonitrile, toluene, xylenes, benzene, mixtures thereof and even an excess of the amide chloride or its parent amide can serve as the solvent. Preferred solvents include: a 1:1 solution of methylene chloride and toluene; dichloroethane or methylene chloride. About three to six equivalents of amide halide per equivalent of lincomycin is used. The preferred ratio is about four or five to one. Conventional means such as evaporation, crystallization and combinations thereof can be used to recover the lincomycin adduct.

15 In some cases an inhibitor, 3-*t*-butyl-4-hydroxy-5-methylphenylsulfide is added to the reaction mixture in an effort to eliminate color from the product and increase yield. This is now regarded to be of questionable advantage.

20 In step (b) the lincomycin adduct is heated to a temperature of about 50 to 75°C for a period of time of about 2 to 40 hrs. to yield a 7-halo-7-deoxy adduct of lincomycin. The temperature of this step will depend upon the particular amide halide used. When the amide halide used is prepared by reacting *N*-formyl piperidine or dimethyl formamide and thionyl chloride the temperature used is about 55 to 25 65°C.

In step (c) the 7-halo-7-deoxy adduct is hydrolyzed by quenching it in a cold solution of base to yield a 7-halo-7-deoxylincomycin. Any aqueous base can be used. The amount of base used should be sufficient to prevent the reaction mixture from becoming strongly 30 acidic. Sodium hydroxide and potassium hydroxide are particularly effective. The product can be recovered by recrystallization, evaporation, extraction, chromatography or combinations thereof.

Starting materials for the process are lincomycin or its analogs and an amide halide prepared by reacting a formamide with reagents 35 such as a thionyl halide, phosgene, oxalyl chloride, phosphorus pentahalide, etc., as described by Eilingsfeld et al, Angew. Chem., above.

Lincomycin is a known antibiotic and methods for preparing it and

its analogs are well known in the art and illustrated in U.S. Patents 3,086,912, and 3,155,580. In addition to those described in the patents cited above analogs of lincomycin are also exemplified in U.S. Patent 3,380,992, and by protected lincomycin and analogs such as methylthiolincosaminide, lincomycin-3,4-acetonide, 3,4-(para-t-butylbenzylidene)-lincomycin, 3,4-cumylidene-lincomycin, and 3,4-benzylidene-lincomycin. As used herein lincomycin or lincomycin analogs means the free base or their salts. The salts may be anhydrous or hydrated.

Amide halides are known and may be prepared by methods well known in the art; "Iminium Salts in Organic Chemistry" Vol. 9, part 2 of Advances in Organic Chemistry, H. Bohme & H.G. Viehe, ed. Wiley (1979). The amide halides used in the process of this invention have the formula III shown in Chart A, wherein hal is bromine or chlorine atom; R<sub>1</sub> and R<sub>2</sub> are the same or different and are selected from the group consisting of aryl, alkyl containing one to eight carbon atoms, inclusive, or the alkyl groups when taken together with the nitrogen atom to which they are attached form (a) heterocyclic rings containing carbon and nitrogen of four to eight ring atoms and (b) morpholino. The term aryl means phenyl, substituted phenyl, naphthyl, substituted naphthyl and other aryl groups that do not interfere with or contain substituents that interfere with the reaction between the amide halide and lincomycin or its analogs. Heterocyclic rings include piperidino, N-substituted piperazino, and pyrrolidino, hexahydroazepino, and octahydroazocino. They can be prepared by reacting a source of halide with a formamide. Sources of halide include thionyl bromide, thionyl chloride, phosgene, oxalyl chloride, phosphorus pentachloride, phosphorus penta-bromide and carbonyl dibromide. In the case of thionyl chloride, the reaction is typically conducted in the presence of a solvent at a temperature of about 30 to 60°C for a period of about 10 min. to 3 hrs. under vacuum. The preferred reaction temperature and times are about 40 to 50°C and 10 minutes to one hr, depending on the vacuum applied. In the process of this invention it is necessary that the conditions used be sufficient to substantially remove the sulfur dioxide from the mixture. It is believed that the presence of residual sulfur dioxide is quite detrimental to the yield and purity of the product. This is assumed to occur because of the formation of a 3,4-sulfite ester, a species taken to be unstable under

the reaction conditions, the structure of which could also detrimentally affect the stereoselectivity of the reaction.

The amide halide can be recovered from the reaction mixture by conventional methods. Thionyl chloride and N-formyl piperidine or  
5 dimethylformamide are the preferred reagents used in the preparation of clindamycin.

The following described examples of the process for preparing 7-halo-deoxylincomycin and intermediates useful therein are indicative of the scope of this invention and are not to be construed as  
10 limitative.

Preparation 1 - N-(Chloromethylene)-piperidinium chloride

Under dry nitrogen a solution of N-formyl piperidine (170 gm, 1.50 mol) in anhydrous diethyl ether (1.5L), stirring rapidly at 5°C,  
15 is treated with gaseous phosgene (142 gm, 1.44 mol) over the course of 1.5 hours. Ice bath cooling is applied to maintain a temperature of less than 12°C. The resulting white solid is filtered off under dry nitrogen, in vacuum, to give 94.4% (228 gm, 1.36 mol) of N-(chloromethylene)-piperidinium chloride.

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Preparation 2 - N-(Chloromethylene)-N-methylmethaninium chloride

Utilizing a procedure similar to that of Preparation 1, but beginning with dimethyl formamide (170 gm, 2.33 mol) and phosgene (228 gm, 2.31 mol), yield (252 gm, 1.97 mol) of N-(chloro-methylene)-N-  
25 methylmethanaminium chloride is obtained.

Preparation 3 - N-(Chloromethylene)-pyrrolidinium chloride

Utilizing a procedure similar to that used in Preparation 1, but beginning with N-formyl pyrrolidine (258 gm, 2.60 mol) and phosgene  
30 (235 gm, 2.47 mol), 96.0% (364 gm, 2.37 mol) of N-(chloromethylene)-pyrrolidinium chloride is obtained.

Preparation 4 - N-(Chloromethylene)-morpholinium chloride

Utilizing a procedure similar that used in Preparation 1, but  
35 beginning with N-formylmorpholine (346 gm, 3.01 mol) and phosgene (301 gm, 3.05 mol), a 65% yield (333 gm, 1.96 mol) of N-(chloromethylene)-morpholinium chloride is obtained.

Preparation 5 - N-(Chloromethylene)-morpholinium chloride

Under dry nitrogen, a solution of N-formyl morpholine (50.6 gm, 440 mmol) in anhydrous diethyl ether (300 ml), stirring rapidly in an ice bath is treated dropwise with a solution of oxalyl chloride (50.8 gm, 400 mmol) in hexane (30 ml). After warming to room temperature for 30 minutes, the solid product is filtered off under dry nitrogen and dried in vacuum to give 91.5% (62.2 gm, 366 mmol) of N-(chloromethylene)-morpholinium chloride.

10 Preparation 6 - N-(Chloromethylene)-piperidinium chloride

Under dry nitrogen, N-formyl piperidine (124 gm, 1.10 mol), rapidly stirring at -4°C, is treated dropwise over the course of 30 minutes with thionyl chloride (144 gm, 1.21 mol), the temperature being maintained below 0°C with ice-methanol cooling. The resulting solution is warmed slowly to 56°C over 80 minutes with the application of vacuum (at about 30 mm). A mixture of methylene chloride 10 ml and toluene (40 ml) is added, and the resulting slurry is concentrated to dryness (37°C, about 30 mm vacuum). This stripping procedure is repeated, and final concentration is accomplished by the application of higher (about 5 mm) vacuum (30°-42°C, 30 min), to yield solid N-(chloromethylene)-morpholinium chloride.

Preparation 7 - N-(Chloromethylene)-N-methylmethaninium chloride

In a manner similar to that used in Preparation 6, dimethyl formamide (32.5 gm, 445 mmol) and thionyl chloride (58.2 gm, 490 mmol) are used to prepare N-(chloromethylene)-N-methylmethanaminium chloride.

Example 1: Clindamycin hydrochloride hydrate

30 (a) Adduct of lincomycin hydrochloride

Under dry nitrogen a slurry of N-(chloromethylene)-piperidinium chloride (36.2 gm, 215 mmol) in dichloroethane (100 ml), while being stirred rapidly and cooled in an ice bath is treated portionwise (15 min) with lincomycin hydrochloride hydrate (18.1 gm, 39.2 mmol), and then with an inhibitor, 3-4-butyl-4-hydroxy-5-methylphenylsulfide (0.17 gm), to yield a solution of an adduct of lincomycin hydrochloride.

(b) Adduct of clindamycin

The resulting mixture obtained in 1(a) is warmed to room temperature for 4 hours, then the temperature is ramped to 60°C over the course of 10 hours. After 4 hours at 60°C, then four hours at 65°C, a mixture containing an adduct of clindamycin is obtained.

5 (c) Clindamycin hydrochloride hydrate

The mixture of the adduct obtained in 1(b) is cooled to 0°C then poured rapidly into sodium hydroxide (17.2 gm, 430 mmol) in water and ice (200 gm), with rapid stirring. The pH is reduced (with hydrochloric acid) to 10.5, and the mixture is stirred at room  
10 temperature two hours, then at pH = 7 overnight. With ice-bath cooling, hydrochloric acid is added to adjust the pH to 1.5. This is then extracted with five (50 ml) portions of methylene chloride, each organic phase being washed in turn with three (75 ml) portions of dilute hydrochloric acid at pH = 1.5. The aqueous phases are  
15 combined, adjusted (with aqueous sodium hydroxide) to pH = 10.5, and extracted with five (50 ml) portions of methylene chloride. Each organic extract is washed sequentially through two (75 ml) portions of 0.5 molar phosphate buffer at pH 6.2. The combined organic phases are dried over sodium sulfate, filtered, and concentrated to an oil. The  
20 oil is taken up in ethyl acetate (200 ml). The solvent is stripped under vacuum, and the stripping procedure is repeated. The resulting oil is taken up in an additional portion of ethyl acetate and subjected to decolorization with 5% activated carbon (0.9 gm Darco G-60, 30 min), filtered (through Celite 454), and reconcentrated to an  
25 oil. This is dissolved in ethyl acetate (81 ml) and ethanol (absolute 23 ml), and concentrated hydrochloric acid is added (with rapid stirring) to a final pH of 0.5. The resulting slurry is stirred for one hour at room temperature, then for 30 minutes at 0°C. The solids are filtered off, washed with ethyl acetate (10 ml), and dried  
30 overnight at 80°C under vacuum to give 93.5% (18.6 gm, 36.6 mmol) of clindamycin hydrochloride ethanol solvate. A portion of this (17.7 gm, 34.9 mmol) is dissolved in water (30 ml), and stripped to a heavy syrup (30 ml). Boiling acetone (415 ml) is added with swirling, the solution is seeded, and stirred while allowing it to cool slowly to  
35 room temperature (4 hr) during the crystallization. After stirring 30 minutes in an ice bath, the white, crystalline product is filtered off and dried in a stream of air to give 96.9% (16.2 gm, 33.8 mmol), giving 90.6% overall, of clindamycin hydrochloride hydrate.



Example 2: Clindamycin hydrochloride hydrate

## (a) Adduct of lincomycin hydrochloride hydrate

Under dry nitrogen, a slurry of N-(chloromethylene)-N-methyl-methaninium chloride prepared in Preparation 2 (22.9 gm, 179 mmol) in dichloroethane (56 ml), stirred rapidly and cooled in an ice bath is treated portionwise (15 min) with lincomycin hydrochloride hydrate (15.0 gm, 32.5 mmol) and then with 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.15 gm) to yield an adduct of lincomycin.

## (b) Clindamycin adduct

The adduct obtained in 2(a) is warmed to room temperature for two hours and then ramped to 60°C over the course of ten hours. After six hours at 60°C then five hours at 68°C, a solution containing an adduct of clindamycin is obtained.

## (c) Clindamycin hydrochloride hydrate

The solution prepared in (b) is cooled to 0°C, then quenched into sodium hydroxide (10.7 gm, 268 mmol) in water and ice (100 gm). The temperature is kept below 21°C by application of an ice-acetone bath, and the pH is maintained above 6 during the quench by the addition of additional aqueous sodium hydroxide. The mixture is stirred at pH = 10.5 at room temperature four two hours, then at pH = 7 overnight.

Work-up and crystallization exactly analogous to that of Example 1, above, gives 90.4% (14.9 gm, 29.4 mmol) of clindamycin hydrochloride ethanol solvate. A portion (14.3 gm, 28.1 mmol) is taken (as above) to clindamycin hydrochloride hydrate in 94.8% yield (12.8 gm, 26.7 mmol), giving 85.7% overall yield.

Example 3: Clindamycin hydrochloride hydrate

## (a) Adduct of lincomycin

Under dry nitrogen, a slurry of N-(chloromethylene)-pyrrolidinium chloride (33.0 gm, 215 mmol) in dichloroethane (80 ml), stirring rapidly and cooled in an ice bath is treated portionwise (20 min) with lincomycin hydrochloride hydrate (18.0 gm, 39.0 mmol) and then with an inhibitor, 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.18 gm), to yield a solution of lincomycin adduct.

## (b) Clindamycin adduct

The solution of lincomycin adduct obtained in 3(a) is warmed to room temperature for an hour, then the temperature is ramped to 60° over the course of 16 hours. After 45 hours at 60° to 65°C, there is

obtained a solution of clindamycin adduct.

(c) Clindamycin hydrochloride hydrate

The solution of adduct obtained in 3(b) is cooled to 0°C, then poured rapidly into sodium hydroxide (15.5 gm, 388 mmol) in water and  
5 ice (200 gm), with rapid stirring. Additional aqueous sodium hydroxide is added to maintain a pH greater than 8. The pH is adjusted to 10.0, the mixture is stirred at room temperature for 3 hours, then the pH is reduced 7.0.

Work-up and crystallization, as above, gives 89.8% (17.8 gm, 35.0  
10 mmol) of clindamycin hydrochloride ethanol solvate. A portion of the solvate (16.8 gm, 32.4 mmol) is taken as in Example 2 to clindamycin hydrochloride hydrate, yielding 94.3% (14.6 gm, 30.5 mmol), giving 84.7% overall yield.

15 Example 4: Clindamycin hydrochloride hydrate

(a) Adduct of lincomycin hydrochloride

Under dry nitrogen, a slurry of the N-(chloromethylene)-morpholinium chloride (37.1 gm, 218 mmol, obtained in Preparation 4) in dichloroethane (90 ml), is treated portionwise with lincomycin  
20 hydrochloride hydrate (18.3 gm, 39.6 mmol) and then with 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.19 gm). Residual solids are washed with dichloroethane (10 ml) and then with methylene chloride (10 ml), to provide a mixture of lincomycin hydrochloride adduct.

(b) Adduct of clindamycin

25 The mixture is warmed to room temperature for 3 hours, then the temperature is ramped to 45°C over the course of 2 hours. After 16 hours at 45°C, then 6 hours at 60°C, the solution is cooled to 0°C.

(c) Clindamycin hydrochloride hydrate

The solution obtained in 4(b) is then poured rapidly into sodium  
30 hydroxide (17.5 gm, 438 mmol) in water and ice (200 gm), with rapid stirring. The pH is reduced (with hydrochloric acid) to 10.5, the mixture stirred at room temperature for 30 minutes, then the pH is reduced further to 1.5.

Work-up and crystallization similar to that of Preparation 2,  
35 above, gives 78.7% (15.8 gm, 31.2 mmol) of clindamycin hydrochloride ethanol solvate. A portion (14.4 gm, 28.4 mmol) is taken (as in Example 1) to clindamycin hydrochloride hydrate in 93.0% yield (12.7 gm, 26.4 mmol), giving 73.1% overall yield.

Example 5: Clindamycin hydrochloride hydrate

## (a) Adduct of lincomycin hydrochloride

Under dry nitrogen, a rapidly stirring slurry of anhydrous lincomycin hydrochloride (10.7 gm, 24.2 mmol) in acetonitrile (15 ml) is treated over the course of an hour with a slurry of N-(chloromethylene)-morpholinium chloride obtained in Preparation 5 (18.3 gm, 109 mmol) in acetonitrile (40 ml) to give lincomycin hydrochloride adduct.

## (b) Clindamycin adduct

The adduct obtained in 5(a) is heated at about 52°C for one hour and then refluxed for 30 minutes to yield the adduct of clindamycin.

## (c) Clindamycin hydrochloride hydrate

The solution of the adduct obtained in 5(b) is cooled to 0° and quenched with anhydrous methanol (30 ml). After stirring at room temperature overnight, then concentrating under vacuum, the residue is taken up in ethyl acetate and washed with cold, aqueous (10%) sodium hydroxide. The aqueous phase is reextracted twice with ethyl acetate, the combined organic phases are dried (magnesium sulfate), filtered, subjected to decolorization with activated carbon (Darco G-60, 0.5 gm, 1 hr), filtered (through Celite 454), and concentrated under vacuum (to 40 gm). Ethyl acetate is added (to a total weight of 63 gm), then anhydrous ethanol (13 ml), and concentrated hydrochloric acid is added dropwise, with rapid stirring to a final pH of 1. After stirring at room temperature one hour, the resulting solid is filtered off and dried under vacuum to constant weight, giving 78.6% (9.66 gm, 19.0 mmol) of clindamycin hydrochloride ethanol solvate. A portion (8.57 gm, 16.9 mmol) is taken (as in Example 1, above), to clindamycin hydrochloride hydrate in 89.3% yield (7.24 gm, 15.1 mmol), giving 70.2% overall yield.

Example 6: Clindamycin hydrochloride hydrate

## (a) Lincomycin hydrochloride adduct

Under dry nitrogen, a mixture of N-(chloromethylene)-piperidinium chloride prepared in Preparation 6 (300 ml), while being stirred rapidly at -4°C, is treated with lincomycin hydrochloride hydrate (80.0 gm, 174 mmol) in portions over the course of 25 minutes, and then 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.80 gm). Residual solids are rinsed in with 50 ml of methylene chloride to provide a

mixture of lincomycin hydrochloride adduct.

(b) Clindamycin adduct

The mixture of lincomycin hydrochloride adduct obtained in 6(a) is heated slowly (30 min) to reflux. Solvent is distilled off, and  
5 toluene (175 ml) is added at an equivalent rate, over the course of 1.5 hours, to a final temperature of 52°C. Refluxing 16 hours brought the temperature to 57°C to obtain a mixture of the adduct of clindamycin.

(c) Clindamycin hydrochloride hydrate

10 The mixture of the adduct obtained in 6(b) is cooled to 0°C and quenched into sodium hydroxide (47.0 gm, 1.18 mmol) in cold water (500 ml). Work-up and crystallization in a manner similar to that used in Example 1, provides 97.2% (85.6 gm, 169 mmol) of clindamycin hydrochloride ethanol solvate. A portion of this (85.1 gm, 168 mmol)  
15 is converted into clindamycin hydrochloride hydrate (as in Example 2) in 93.0% yield (74.8 gm, 156 mmol), giving 90.4% overall.

Example 7: Clindamycin hydrochloride hydrate

In a manner similar to that used in Example 6, N-(chloromethyl-  
20 ene)-methylmethanaminium is used to convert lincomycin hydrochloride hydrate (32.8 gm, 71.2 mmol) into clindamycin hydrochloride ethanol solvate in 88.9% yield (32.1 gm, 63.3 mmol). A portion of this (30.5 gm, 60.6 mmol), is converted into clindamycin hydrochloride hydrate (as above) in 90.1% yield (25.9 gm, 54.1 mmol) giving 80.1% overall  
25 yield.

Example 8: Clindamycin hydrochloride hydrate

In a procedure similar to that used in Example 6, but substitut-  
ing substantially anhydrous lincomycin hydrochloride (containing 1.3%  
30 water by Karl Fischer titration) for lincomycin hydrochloride hydrate there is obtained clindamycin hydrochloride hydrate in 86.0% overall yield.

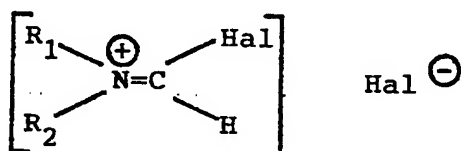
Example 9:

35 Utilizing a procedure similar to that used in Examples 1 through 9 but substituting the following for lincomycin:

methylthiolincosaminide,

~~lincomycin-3,4-acetonide,~~

(a) reacting a starting compound selected from lincomycin and analogues thereof, with an amide halide  
5 having the formula



5. A process according to claim 3, wherein the amide chloride is N-(chloromethylene)-N-methylmethanaminium chloride and the starting compound is hydrated lincomycin hydrochloride.

6. A process according to claim 3, wherein the amide chloride is N-(chloromethylene)piperidinium chloride and the starting compound is hydrated lincomycin hydrochloride.

- 5 7. A process according to claim 5 or 6, for preparing clindamycin hydrochloride hydrate, wherein the starting compound is lincomycin hydrochloride hydrate.

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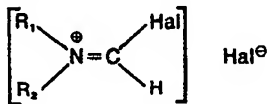
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wherein each Hal is bromine or chlorine, and either R<sub>1</sub> and  
R<sub>2</sub> are independently selected from aryl and C<sub>1-8</sub> alkyl or  
NR<sub>1</sub>R<sub>2</sub> is morpholino or a heterocyclic ring containing 4 to 8  
ring atoms selected from carbon and nitrogen, to form an  
adduct;

(b) heating the adduct, to form a 7-halo-7-deoxy adduct;  
and

(c) hydrolysing the 7-halo-7-deoxy adduct with an  
aqueous base.

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European Patent  
Office

# EUROPEAN SEARCH REPORT

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Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y,D	US-A-3 496 163 (R.D. BIRKENMEYER) * Column 10, lines 42-51,65-72 *	1-7	C 07 H 15/16 C 07 C 119/18 C 07 D 295/18
Y	--- M. FIESER et al.: "Reagents for organic synthesis", vol. 3, 1972, page 116, Wiley-Interscience, New York, US; * Page 116 * & TETRAHEDRON LETTERS, page 165, 1969	1-7	
Y	--- L.F. FIESER et al.: "Reagents for organic synthesis", 1967, pages 286-289, John Wiley and Sons Inc, New York, US * Page 286 *	1-7	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 H 15/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 17-03-1987	Examiner VERHULST W.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	





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56 References cited:  
US-A-3 496 163

M. FIESER et al.: "Reagents for organic  
synthesis", vol. 3, 1972, page 116, Wiley-  
Interscience, New York, US;

L.F. FIESER et al.: "Reagents for organic  
synthesis", 1967, pages 286-289, John Wiley and  
Sons Inc, New York, US

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## Description

The present invention relates to a process for preparing 7-halo-7-deoxylincomycins (including clindamycin) from lincomycin and analogues thereof. Clindamycin is a well-known antibiotic.

US—A—3435025, US—A—3496163 and US—A—3509127 disclose such a process, in which the 7-hydroxyl group of the starting compound, i.e. lincomycin or an analogue thereof, is replaced with a halogen group, by reaction with a Rydon reagent and heating the resulting product. The use of thionyl chloride for such a process is described in US—A—3496163, US—A—3509127 and US—A—3574186. A process for preparing 7-halo-7-deoxylincomycin by the use of a sulfite-protected lincomycin and Rydon reagents is described in US—A—3714141.

The use of a Vilsmeier reagent to substitute a halo atom for a hydroxyl group is described by Eillingsfeld *et al*, Angew. Chem. 72 (1960) 836, and Chem. Ber. 96 (1963) 2671. Evans *et al*, JOC 33 (1968) 1074, disclose that, while a Vilsmeier reagent prepared from methanesulfonyl chloride and dimethylformamide was successfully used to replace a primary hydroxyl group, it was not successful in attempts to replace a secondary hydroxyl group.

The structure of the adduct formed between dimethylformamide and thionyl chloride has been investigated by Ferre *et al*, Tet. Lett. (1969) 2161. Conditions for converting the adduct to the corresponding amide chloride have been described by Kikagawa *et al*, Chem. Pharm. Bull. 19 (1971) 2629. Bosshard *et al*, Helv. Chim. Acta. 42 (1959) 16153, disclose the use of dimethylformamide as a catalyst in the conversion of carboxylic acids to acid chlorides.

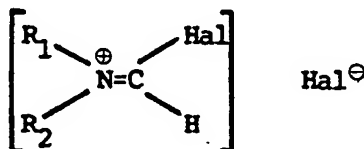
Hepburn *et al*, J. Chem. Soc. Perkin I (1976) 754, and Chem. & Ind. (1974) 664, describe the use of amide chlorides obtained from Vilsmeier reagents, to replace hydroxyl groups by chlorine or bromine groups. The hydroxyl-containing compounds were relatively simple alcohols.

The use of a mixture of mesyl chloride and dimethylformamide to replace primary groups of hexopyranosides by chlorine, is described by Edwards *et al*, Tet. Lett. (1973) 2369. The 5'-halogenation of nucleosides by amide chlorides is described by Dobs *et al*, Tet. Lett. (1969) 165.

It is unclear, from the prior art, as to whether the Vilsmeier reagent is more generally effective than the amide chloride, the result of removing sulphur dioxide.

According to the present invention, a process for preparing 7-halo-7-deoxylincomycin or an analogue thereof comprises

(a) reacting a starting compound selected from lincomycin and analogues thereof, with an amide halide having the formula



wherein each Hal is bromine or chlorine, and either R<sub>1</sub> and R<sub>2</sub> are independently selected from aryl and C<sub>1-8</sub> alkyl or NR<sub>1</sub>R<sub>2</sub> is morpholino or a heterocyclic ring containing 4 to 8 ring atoms selected from carbon and nitrogen, to form an adduct;

(b) heating the adduct, to form a 7-halo-7-deoxy adduct; and

(c) hydrolysing the 7-halo-7-deoxy adduct with an aqueous base.

One advantage of the novel process is that the use of an amide halide, rather than a Vilsmeier reagent, gives increased yields and reduced amounts of by-products. Another advantage is that hydrated lincomycin can be used without detrimentally affecting the yield or quality of the product.

The starting compound is preferably lincomycin. Examples of analogues which can be used are methylthiolincosaminide, lincomycin-3,4-acetonide, 3,4-cumylidenelincomycin, 3,4-(p-t-butylbenzylidene)lincomycin and 3,4-benzylidenelincomycin. The product of the process is preferably clindamycin. Examples of analogues, prepared using the starting compounds exemplified immediately above, are 7-chloromethylthiolincosaminide, clindamycin-3,4-acetonide, 3,4-cumylideneclindamycin, 3,4-(p-t-butylbenzylidene)clindamycin and 3,4-benzylideneclindamycin.

In step (a), lincomycin or an analogue thereof, either in its free form or as an anhydrous or hydrated salt, is reacted with an amide halide. Amide chlorides, especially those prepared from N-formylpiperidine and dimethylformamide, are preferred. The reaction is conducted in the presence of a solvent at -10 to 40°C for a reaction time of about several minutes to several hours. Preferred reaction temperatures and times are about 0° to 5°C and 10 to 30 minutes, respectively. Solvents that can be used include chlorinated hydrocarbons such as methylene chloride, 1,2-dichloroethane; various chlorinated aromatics (i.e. chlorobenzene, dichlorobenzene, etc.); acetonitrile, toluene, xylenes, benzene, mixtures thereof and even an excess of the amide chloride or its parent amide can serve as the solvent. Preferred solvents include: a 1:1 solution of methylene chloride and toluene; dichloroethane or methylene chloride. About three to six equivalents of amide halide per equivalent of lincomycin is used. The preferred ratio is about

four or five to one. Conventional means such as evaporation, crystallization and combinations thereof can be used to recover the lincomycin adduct.

In some cases an inhibitor, 3-t-butyl-4-hydroxy-5-methylphenylsulfide is added to the reaction mixture in an effort to eliminate color from the product and increase yield. This is now regarded to be of questionable advantage.

In step (b) the lincomycin adduct is heated to a temperature of about 50 to 75°C for a period of time of about 2 to 40 hrs. to yield a 7-halo-7-deoxy adduct of lincomycin. The temperature of this step will depend upon the particular amide halide used. When the amide halide used is prepared by reacting N-formyl piperidine or dimethyl formamide and thionyl chloride the temperature used is about 55 to 65°C.

In step (c) the 7-halo-7-deoxy adduct is hydrolyzed by quenching it in a cold solution of base to yield a 7-halo-7-deoxylincomycin. Any aqueous base can be used. The amount of base used should be sufficient to prevent the reaction mixture from becoming strongly acidic. Sodium hydroxide and potassium hydroxide are particularly effective. The product can be recovered by recrystallization, evaporation, extraction, chromatography or combinations thereof.

Starting materials for the process are lincomycin or its analogs and an amide halide prepared by reacting a formamide with reagents such as thionyl halide, phosgene, oxalyl chloride, phosphorus pentahalide etc., as described by Eilingsfeld et al, Angew. Chem., above.

Lincomycin is a known antibiotic and methods for preparing it and its analogs are well known in the art and illustrated in U.S. Patents 3,086,912, and 3,155,580. In addition to those described in the patents cited above analogs of lincomycin are also exemplified in U.S. Patent 3,380,992, and by protected lincomycin and analogs such as methylthiolincosaminide, lincomycin-3,4-acetonide, 3,4-(para-t-butylbenzylidene)-lincomycin, 3,4-cumylidene-lincomycin, and 3,4-benzylidene-lincomycin. As used herein lincomycin or lincomycin analogs means the free base or their salts. The salts may be anhydrous or hydrated.

Amide halides are known and may be prepared by methods well known in the art; "Iminium Salts in Organic Chemistry" Vol. 9, part 2 of Advances in Organic Chemistry, H. Bohme & H. G. Viehe, ed. Wiley (1979). The amide halides used in the process of this invention have the formula III shown in Chart A, wherein hal is bromine or chlorine atom; R<sub>1</sub> and R<sub>2</sub> are the same or different and are selected from the group consisting of aryl, alkyl containing one to eight carbon atoms, inclusive, or the alkyl groups when taken together with the nitrogen atom to which they are attached form (a) heterocyclic rings containing carbon and nitrogen of four to eight ring atoms and (b) morpholino. The term aryl means phenyl, substituted phenyl, naphthyl, substituted naphthyl and other aryl groups that do not interfere with or contain substituents that interfere with the reaction between the amide halide and lincomycin or its analogs. Heterocyclic rings include piperidino, N-substituted piperazino, and pyrrolidino, hexahydroazepino, and octahydroazocino. They can be prepared by reacting a source of halide with a formamide. Sources of halide include thionyl bromide, thionyl chloride, phosgene, oxalyl chloride, phosphorus pentachloride, phosphorus penta-bromide and carbonyl dibromide. In the case of thionyl chloride, the reaction is typically conducted in the presence of a solvent at a temperature of about 30 to 60°C for a period of about 10 min. to 3 hrs. under vacuum. The preferred reaction temperature and times are about 40 to 50°C and 10 minutes to one hr, depending on the vacuum supplied. In the process of this invention it is necessary that the conditions used be sufficient to substantially remove the sulfur dioxide from the mixture. It is believed that the presence of residual sulfur dioxide is quite detrimental to the yield and purity of the product. This is assumed to occur because of the formation of a 3,4-sulfite ester, a species taken to be unstable under the reaction conditions, the structure of which could also detrimentally affect the stereoselectivity of the reaction.

The amide halide can be recovered from the reaction mixture by conventional methods. Thionyl chloride and N-formyl piperidine or dimethylformamide are the preferred reagents used in the preparation of clindamycin.

The following described examples of the process for preparing 7-halo-deoxylincomycin and intermediates useful therein are indicative of the scope of this invention and are not to be construed as limitative.

#### Preparation 1

##### N-(Chloromethylene)-piperidinium chloride

Under dry nitrogen a solution of N-formyl piperidine (170 gm, 1.50 mol) in anhydrous diethyl ether (1.5 L), stirring rapidly at 5°C, is treated with gaseous phosgene (142 gm, 1.44 mol) over the course of 1.5 hours. Ice bath cooling is applied to maintain a temperature of less than 12°C. The resulting white solid is filtered off under dry nitrogen, in vacuum, to give 94.4% (288 gm, 1.36 mol) of N-(chloromethylene)-piperidinium chloride.

#### Preparation 2

##### N-(Chloromethylene)-N-methylmethaninium chloride

Utilizing a procedure similar to that used in Preparation 1, but beginning with dimethyl formamide (170 gm, 2.33 mol) and phosgene (228 gm, 2.31 mol), yield (252 gm, 1.97 mol) of N-(chloro-methylene)-N-methylmethanaminium chloride is obtained.

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### Preparation 3

#### N-(Chloromethylene)-pyrrolidinium chloride

Utilizing a procedure similar to that used in Preparation 1, but beginning with N-formyl pyrrolidine (258 gm, 2.60 mol) and phosgene (235 gm, 2.47 mol), 96.0% (364 gm, 2.37 mol) of N-(chloromethylene)-pyrrolidinium chloride is obtained.

### Preparation 4

#### N-(Chloromethylene)-morpholinium chloride

Utilizing a procedure similar to that used in Preparation 1, but beginning with N-formylmorpholine (346 gm, 3.01 mol) and phosgene (301 gm, 3.05 mol), a 65% yield (333 gm, 1.96 mol) of N-(chloromethylene)-morpholinium chloride is obtained.

### Preparation 5

#### N-(Chloromethylene)-morpholinium chloride

Under dry nitrogen, a solution of N-formyl morpholine (50.6 gm, 440 mmol) in anhydrous diethyl ether (300 ml), stirring rapidly in an ice bath is treated dropwise with a solution of oxalyl chloride (50.8 gm, 400 mmol) in hexane (30 ml). After warming to room temperature for 30 minutes, the solid product is filtered off under dry nitrogen and dried in vacuum to give 91.5% (62.2 gm, 366 mmol) of N-(chloromethylene)-morpholinium chloride.

### Preparation 6

#### N-(Chloromethylene)-piperidinium chloride

Under dry nitrogen, N-formyl piperidine (124 gm, 1.10 mol), rapidly stirring at  $-4^{\circ}\text{C}$ , is treated dropwise over the course of 30 minutes with thionyl chloride (144 gm, 1.21 mol), the temperature being maintained below  $0^{\circ}\text{C}$  with ice-methanol cooling. The resulting solution is warmed slowly to  $56^{\circ}\text{C}$  over 80 minutes with the application of vacuum (at about 30 mm). A mixture of methylene chloride 10 ml and toluene (40 ml) is added, and the resulting slurry is concentrated to dryness ( $37^{\circ}\text{C}$ , about 30 mm vacuum). This stripping procedure is repeated, and final concentration is accomplished by the application of higher (about 5 mm) vacuum ( $30^{\circ}\text{--}42^{\circ}\text{C}$ , 30 min), to yield solid N-(chloromethylene)-morpholinium chloride.

### Preparation 7

#### N-(Chloromethylene)-N-methylmethaninium chloride

In a manner similar to that used in Preparation 6, dimethyl formamide (32.5 gm, 445 mmol) and thionyl chloride (58.2 gm, 490 mmol) are used to prepare N-(chloromethylene)-N-methylmethanaminium chloride.

### Example 1

#### Clindamycin hydrochloride hydrate

##### (a) Adduct of lincomycin hydrochloride

Under dry nitrogen a slurry of N-(chloromethylene)-piperidinium chloride (36.2 gm, 215 mmol) in dichloroethane (100 ml), while being stirred rapidly and cooled in an ice bath is treated portionwise (15 min) with lincomycin hydrochloride hydrate (18.1 gm, 39.2 mmol), and then with an inhibitor, 3-4-butyl-4-hydroxy-5-methylphenylsulfide (0.17 gm), to yield a solution of an adduct of lincomycin hydrochloride.

##### (b) Adduct of clindamycin

The resulting mixture obtained in 1(a) is warmed to room temperature for 4 hours, then the temperature is ramped to  $60^{\circ}\text{C}$  over the course of 10 hours. After 4 hours at  $60^{\circ}\text{C}$ , then four hours at  $65^{\circ}\text{C}$ , a mixture containing an adduct of clindamycin is obtained.

##### (c) Clindamycin hydrochloride hydrate

The mixture of the adduct obtained in 1(b) is cooled to  $0^{\circ}\text{C}$  then poured rapidly into sodium hydroxide (17.2 gm, 430 mmol) in water and ice, (200 gm), with rapid stirring. The pH is reduced (with hydrochloric acid) to 10.5, and the mixture is stirred at room temperature two hours, then at pH = 7 overnight. With ice-bath cooling, hydrochloric acid is added to adjust the pH to 1.5. This is then extracted with five (50 ml) portions of methylene chloride, each organic phase being washed in turn with three (75 ml) portions of dilute hydrochloric acid at pH = 1.5. The aqueous phases are combined, adjusted (with aqueous sodium hydroxide) to pH = 10.5, and extracted with five (50 ml) portions of methylene chloride. Each organic extract is washed sequentially through two (75 ml) portions of 0.5 molar phosphate buffer at pH 6.2. The combined organic phases are dried over sodium sulfate, filtered, and concentrated to an oil. The oil is taken up in ethyl acetate (200 ml). The solvent is stripped under vacuum, and the stripping procedure is repeated. The resulting oil is taken up in an additional portion of ethyl acetate and subjected to decolorization with 5% activated carbon (0.9 gm Darco G-60, 30 min), filtered (through Celite 454), and reconcentrated to an oil. This is dissolved in ethyl acetate (81 ml) and ethanol (absolute 23 ml), and concentrated hydrochloric acid is added (with rapid stirring) to a final pH of 0.5. The resulting slurry is stirred for one hour at room temperature, then for 30 minutes at  $0^{\circ}\text{C}$ . The solids are filtered off, washed with ethyl acetate (10 ml), and dried overnight at  $80^{\circ}\text{C}$  under vacuum to give 93.5% (18.6 gm, 36.6 mmol) of clindamycin hydrochloride ethanol solvate. A portion of this (17.7 gm, 34.9 mmol) is dissolved in water (30 ml), and stripped to a heavy

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5 syrup (30 ml). Boiling acetone (415 ml) is added with swirling, the solution is seeded, and stirred while allowing it to cool slowly to room temperature (4 hr) during the crystallization. After stirring 30 minutes in an ice bath, the white, crystalline product is filtered off and dried in a stream of air to give 96.9% (16.2 gm, 33.8 mmol), giving 90.6% overall, of clindamycin hydrochloride hydrate.

### Example 2

#### Clindamycin hydrochloride hydrate

##### (a) Adduct of lincomycin hydrochloride hydrate

10 Under dry nitrogen, a slurry of N-(chloromethylene)-N-methylmethaninium chloride prepared in Preparation 2 (22.9 gm, 179 mmol) in dichloroethane (56 ml), stirred rapidly and cooled in an ice bath is treated portionwise (15 min) with lincomycin hydrochloride hydrate (15.0 gm, 32.5 mmol) and then with 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.15 gm) to yield an adduct of lincomycin.

##### (b) Clindamycin adduct

15 The adduct obtained in 2(a) is warmed to room temperature for two hours and then ramped to 60°C over the course of ten hours. After six hours at 60°C then five hours at 68°C, a solution containing an adduct of clindamycin is obtained.

##### (c) Clindamycin hydrochloride hydrate

20 The solution prepared in (b) is cooled to 0°C, then quenched into sodium hydroxide (10.7 gm, 268 mmol) in water and ice (100 gm). The temperature is kept below 21°C by application of an ice-acetone bath, and the pH is maintained above 6 during the quench by the addition of additional aqueous sodium hydroxide. The mixture is stirred at pH = 10.5 at room temperature for two hours, then at pH = 7 overnight.

25 Work-up and crystallization exactly analogous to that of Example 1, above, gives 90.4% (14.9 gm, 29.4 mmol) of clindamycin hydrochloride ethanol solvate. A portion (14.3 gm, 28.1 mmol) is taken (as above) to clindamycin hydrochloride hydrate in 94.8% yield (12.8 gm, 26.7 mmol), giving 85.7% overall yield.

### Example 3

#### Clindamycin hydrochloride hydrate

##### (a) Adduct of lincomycin

30 Under dry nitrogen, a slurry of N-(chloromethylene)-pyrrolidinium chloride (33.0 gm, 215 mmol) in dichloroethane (80 ml), stirring rapidly and cooled in an ice bath is treated portionwise (20 min) with lincomycin hydrochloride hydrate (18.0 gm, 39.0 mmol) and then with an inhibitor, 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.18 gm), to yield a solution of lincomycin adduct.

##### (b) Clindamycin adduct

35 The solution of lincomycin adduct obtained in 3(a) is warmed to room temperature for an hour, then the temperature is ramped to 60°C over the course of 16 hours. After 45 hours at 60° to 65°C. there is obtained a solution of clindamycin adduct.

##### (c) Clindamycin hydrochloride hydrate

40 The solution of adduct obtained in 3(b) is cooled to 0°C, then poured rapidly into sodium hydroxide (15.5 gm, 388 mmol) in water and ice (200 gm), with rapid stirring. Additional aqueous sodium hydroxide is added to maintain a pH greater than 8. The pH is adjusted to 10.0, the mixture is stirred at room temperature for 3 hours, and then the pH is reduced to 7.0.

45 Work-up and crystallization, as above, gives 89.8% (17.8 gm, 35.0 mmol) of clindamycin hydrochloride ethanol solvate. A portion of the solvate (16.8 gm, 32.4 mmol) is taken as in Example 2 to clindamycin hydrochloride hydrate, yielding 94.3% (14.6 gm, 30.5 mmol), giving 84.7% overall yield.

### Example 4

#### Clindamycin hydrochloride hydrate

##### (a) Adduct of lincomycin hydrochloride

50 Under dry nitrogen, a slurry of N-(chloromethylene)-morpholinium chloride (37.1 gm, 218 mmol, obtained in Preparation 4) in dichloroethane (90 ml), is treated portionwise with lincomycin hydrochloride hydrate (15.3 gm, 39.6 mmol) and then with 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.19 gm). Residual solids are washed with dichloroethane (10 ml) and then with methylene chloride (10 ml), to provide a mixture of lincomycin hydrochloride adduct.

##### (b) Adduct of clindamycin

60 The mixture is warmed to room temperature for 3 hours, then the temperature is ramped to 45°C over the course of 2 hours. After 16 hours at 45°C, then 6 hours at 60°C, the solution is cooled to 0°C.

##### (c) Clindamycin hydrochloride hydrate

65 The solution obtained in 4(b) is poured rapidly into sodium hydroxide (17.5 gm, 438 mmol) in water and ice (200 gm) with rapid stirring. The pH is reduced (with hydrochloric acid) to 10.5, the mixture stirred at

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room temperature for 30 minutes, then the pH is reduced further to 1.5.

Work-up and crystallization similar to that of Preparation 2, above, gives 78.7% (15.8 gm, 31.2 mmol) of clindamycin hydrochloride ethanol solvate. A portion (14.4 gm, 28.4 mmol) is taken (as in Example 1) to clindamycin hydrochloride hydrate in 93.0% yield (12.7 gm, 26.4 mmol), giving 73.1% overall yield.

### Example 5

#### Clindamycin hydrochloride hydrate

##### (a) Adduct of lincomycin hydrochloride

Under dry nitrogen, a rapidly stirring slurry of anhydrous lincomycin hydrochloride (10.7 gm, 24.2 mmol) in acetonitrile (15 ml) is treated over the course of an hour with a slurry of N-(chloromethylene)-morpholinium chloride obtained in Preparation 5 (18.3 gm, 109 mmol) in acetonitrile (40 ml) to give lincomycin hydrochloride adduct.

##### (b) Clindamycin adduct

The adduct obtained in 5(a) is heated at about 52°C for one hour and then refluxed for 30 minutes to yield the adduct of clindamycin.

##### (c) Clindamycin hydrochloride hydrate

The solution of the adduct obtained in 5(b) is cooled to 0° and quenched with anhydrous methanol (30 ml). After stirring at room temperature overnight, then concentrating under vacuum, the residue is taken up in ethyl acetate and washed with cold, aqueous (10%) sodium hydroxide. The aqueous phase is reextracted twice with ethyl acetate, the combined organic phases are dried (magnesium sulfate), filtered, subjected to decolorization with activated carbon (Darco G—60, 0.5 gm, 1 hr), filtered (through Celite 454), and concentrated under vacuum (40 gm). Ethyl acetate is added (to a total weight of 63 gm), then anhydrous ethanol (13 ml), and concentrated hydrochloric acid is added dropwise, with rapid stirring to a final pH of 1. After stirring at room temperature for one hour, the resulting solid is filtered off and dried under vacuum to constant weight, giving 78.6% (9.66 gm, 19.0 mmol) of clindamycin hydrochloride ethanol solvate. A portion (8.57 gm, 16.9 mmol) is taken (as in Example 1, above), to clindamycin hydrochloride hydrate in 89.3% yield (7.24 gm, 15.1 mmol), giving 70.2% overall yield.

### Example 6

#### Clindamycin hydrochloride hydrate

##### (a) Lincomycin hydrochloride adduct

Under dry nitrogen, a mixture of N-(chloromethylene)-piperidinium chloride prepared in Preparation 6 (300 ml), while being stirred rapidly at -4°C, is treated with lincomycin hydrochloride hydrate (80.0 gm, 174 mmol) in portions over the course of 25 minutes, and then 3-t-butyl-4-hydroxy-5-methylphenyl sulfide (0.80 gm). Residual solids are rinsed in with 50 ml of methylene chloride to provide a mixture of lincomycin hydrochloride adduct.

##### (b) Clindamycin adduct

The mixture of lincomycin hydrochloride adduct obtained in 6(a) is heated slowly (30 min) to reflux. Solvent is distilled off, and toluene (175 ml) is added at an equivalent rate, over the course of 1.5 hours to a final temperature of 52°C. Refluxing 16 hours brought the temperature to 57°C to obtain a mixture of the adduct of clindamycin

##### (c) Clindamycin hydrochloride hydrate

The mixture of the adduct obtained in 6(b) is cooled to 0°C and quenched into sodium hydroxide (47.0 gm, 1.18 mmol) in cold water (500 ml). Work-up and crystallization in a manner similar to that used in Example 1, provides 97.2% (85.6 gm, 169 mmol) of clindamycin hydrochloride ethanol solvate. A portion of this (85.1 gm, 168 mmol) is converted into clindamycin hydrochloride hydrate (as in Example 2) in 93.0% yield (74.8 gm, 156 mmol), giving 90.4% overall.

### Example 7

#### Clindamycin hydrochloride hydrate

In a manner similar to that used in Example 6, N-(chloromethylene)-methylethylmethanaminium is used to convert lincomycin hydrochloride hydrate (32.8 gm, 71.2 mmol) into clindamycin hydrochloride ethanol solvate in 88.9% yield (32.1 gm, 63.3 mmol). A portion of this (30.5 gm, 60.6 mmol) is converted into clindamycin hydrochloride hydrate (as above) in 90.1% yield (25.9 gm, 54.1 mmol) giving 80.1% overall yield.

### Example 8

#### Clindamycin hydrochloride hydrate

In a procedure similar to that used in Example 6, but substituting substantially anhydrous lincomycin hydrochloride (containing 1.3% water by Karl Fischer titration) for lincomycin hydrochloride hydrate there is obtained clindamycin hydrochloride hydrate in 86.0% overall yield.

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Claims for the Contracting States: BE CH DE FR GB IT LU NL SE

1. A process for preparing 7-halo-7-deoxylincomycin or an analogue thereof, which comprises  
 (a) reacting a starting compound selected from lincomycin and analogues thereof, with an amide  
 5 halide having the formula



wherein each Hal is bromine or chlorine, and either R<sub>1</sub> and R<sub>2</sub> are independently selected from aryl and C<sub>1-8</sub>  
 15 alkyl or NR<sub>1</sub>R<sub>2</sub> is morpholino or a heterocyclic ring containing 4 to 8 ring atoms selected from carbon and nitrogen, to form an adduct;

- (b) heating the adduct, to form a 7-halo-7-deoxy adduct; and  
 (c) hydrolysing the 7-halo-7-deoxy adduct with an aqueous base.  
 2. A process according to claim 1, wherein the amide halide is an amide chloride.  
 3. A process according to claim 1, wherein the amide chloride is selected from N-(chloromethylene)-N-  
 20 methylmethanaminium chloride, N-(chloromethylene)piperidinium chloride, N-(chloromethylene)morpholinium chloride and N-(chloromethylene)pyrrolidinium chloride.  
 4. A process according to any preceding claim, for preparing clindamycin, wherein the starting compound is lincomycin.  
 5. A process according to claim 3, wherein the amide chloride is N-(chloromethylene)-N-  
 25 methylmethanaminium chloride and the starting compound is hydrated lincomycin hydrochloride.  
 6. A process according to claim 3, wherein the amide chloride is N-(chloromethylene)piperidinium chloride and the starting compound is hydrated lincomycin hydrochloride.  
 7. A process according to claim 5 or 6, for preparing clindamycin hydrochloride hydrate, wherein the  
 30 starting compound is lincomycin hydrochloride hydrate.  
 8. An adduct of lincomycin or an analogue thereof and an amide halide as defined in any of claims 1 to 3.  
 9. An adduct of lincomycin and an amide halide as defined in any of claims 1 to 3.  
 10. An adduct of lincomycin hydrochloride hydrate and an amide chloride as defined in claim 5 or claim  
 35 6.

Claims for the Contracting State: AT

1. A process for preparing 7-halo-7-deoxylincomycin or an analogue thereof, which comprises  
 40 (a) reacting a starting compound selected from lincomycin and analogues thereof, with an amide halide having the formula



wherein each Hal is bromine or chlorine, and either R<sub>1</sub> and R<sub>2</sub> are independently selected from aryl and C<sub>1-8</sub>  
 50 alkyl or NR<sub>1</sub>R<sub>2</sub> is morpholino or a heterocyclic ring containing 4 to 8 ring atoms selected from carbon and nitrogen, to form an adduct;

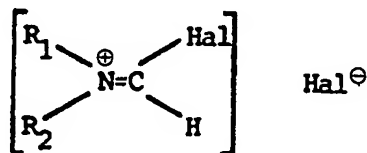
- (b) heating the adduct, to form a 7-halo-7-deoxy adduct; and  
 (c) hydrolysing the 7-halo-7-deoxy adduct with an aqueous base.  
 2. A process according to claim 1, wherein the amide halide is an amide chloride.  
 3. A process according to claim 1, wherein the amide chloride is selected from N-(chloromethylene)-N-  
 55 methylmethanaminium chloride, N-(chloromethylene)piperidinium chloride, N-(chloromethylene)morpholinium chloride and N-(chloromethylene)pyrrolidinium chloride.  
 4. A process according to any preceding claim, for preparing clindamycin, wherein the starting compound is lincomycin.  
 5. A process according to claim 3, wherein the amide chloride is N-(chloromethylene)-N-  
 60 methylmethanaminium chloride and the starting compound is hydrated lincomycin hydrochloride.  
 6. A process according to claim 3, wherein the amide chloride is N-(chloromethylene)piperidinium chloride and the starting compound is hydrated lincomycin hydrochloride.  
 7. A process according to claim 5 or 6, for preparing clindamycin hydrochloride hydrate, wherein the  
 65 starting compound is lincomycin hydrochloride hydrate.

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Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LU NL SE

1. Verfahren zur Herstellung von 7-Halo-7-deoxylincomycin oder einem Analogen davon, welches folgende Schritte umfaßt:

(a) Umsetzen einer Ausgangsverbindung, gewählt aus Lincomycin oder Analogen davon, mit einem Amidhalogenid der Formel



worin jedes Hal Brom oder Chlor bedeutet und sowohl  $R_1$ , als auch  $R_2$  unabhängig voneinander aus Aryl und  $C_{1-8}$  Alkyl gewählt ist oder  $NR_1R_2$  Morpholin oder einen heterocyclischen Ring mit 4 bis 8 Ringatom, gewählt aus Kohlenstoff und Stickstoff bedeutet, um ein Addukt zu bilden;

(b) Erhitzen des Addukts um ein 7-Halo-7-deoxyaddukt zu bilden und

(c) Hydrolysieren des 7-Halo-7-deoxyaddukts mit einer wäßrigen Base.

2. Verfahren nach Anspruch 1, worin das Amidhalogenid Amidchlorid ist.

3. Verfahren nach Anspruch 1, worin das Amidchlorid aus N-(Chlormethylen)-N-methylmethanaminiumchlorid, N-(Chlormethylen)piperidiniumchlorid, N-(Chlormethylen)morpholiniumchlorid und N-(Chlormethylen)pyrrolidiniumchlorid gewählt ist.

4. Verfahren nach einem der vorhergehenden Ansprüche zur Herstellung von Clindamycin, worin die Ausgangsverbindung Lincomycin ist.

5. Verfahren nach Anspruch 3, worin das Amidchlorid N-(Chlormethylen)-N-methylmethanaminiumchlorid ist und die Ausgangsverbindung wasserhaltiges Lincomycinhydrochlorid ist.

6. Verfahren nach Anspruch 3, worin das Amidchlorid N-(Chlormethylen)piperidiniumchlorid ist und die Ausgangsverbindung wasserhaltiges Lincomycinhydrochlorid ist.

7. Verfahren nach Anspruch 5 oder 6, zur Herstellung von Clindamycinhydrochlorid.Hydrat, worin die Ausgangsverbindung Lincomycinhydrochlorid.Hydrat ist.

8. Lincomycinaddukt oder ein Analoges davon und ein Amidhalogenid, wie in einem der Ansprüche 1 bis 3 definiert.

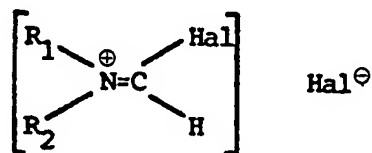
9. Lincomycinaddukt und ein Amidhalogenid, wie in einem der Ansprüche 1 bis 3 definiert.

10. Lincomycinhydrochlorid.Hydrat-Addukt und ein Amidchlorid, wie in einem der Ansprüche 5 oder 6 definiert.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung von 7-Halo-7-deoxylincomycin oder einem Analogen davon, welches folgende Schritte umfaßt:

(a) Umsetzen einer Ausgangsverbindung, gewählt aus Lincomycin oder Analogen davon, mit einem Amidhalogenid der Formel



worin jedes Hal Brom oder Chlor bedeutet und sowohl  $R_1$ , als auch  $R_2$  unabhängig voneinander aus Aryl und  $C_{1-8}$  Alkyl gewählt ist oder  $NR_1R_2$  Morpholin oder einen heterocyclischen Ring mit 4 bis 8 Ringatom, gewählt aus Kohlenstoff und Stickstoff bedeutet, um ein Addukt zu bilden;

(b) Erhitzen des Addukts um ein 7-Halo-7-deoxyaddukt zu bilden und

(c) Hydrolysieren des 7-Halo-7-deoxyaddukts mit einer wäßrigen Base.

2. Verfahren nach Anspruch 1, worin das Amidhalogenid Amidchlorid ist.

3. Verfahren nach Anspruch 1, worin das Amidchlorid aus N-(Chlormethylen)-N-methylmethanaminiumchlorid, N-(Chlormethylen)piperidiniumchlorid, N-(Chlormethylen)morpholiniumchlorid und N-(Chlormethylen)pyrrolidiniumchlorid gewählt ist.

4. Verfahren nach einem der vorhergehenden Ansprüche zur Herstellung von Clindamycin, worin die Ausgangsverbindung Lincomycin ist.

5. Verfahren nach Anspruch 3, worin das Amidchlorid N-(Chlormethylen)-N-methylmethanaminiumchlorid ist und die Ausgangsverbindung wasserhaltiges Lincomycinhydrochlorid ist.



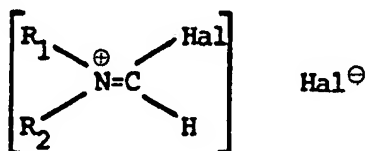
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6. Verfahren nach Anspruch 3, worin das Amidchlorid N-(Chlormethylen)piperidiniumchlorid ist und die Ausgangsverbindung wasserhaltiges Lincomycinhydrochlorid ist.

7. Verfahren nach Anspruch 5 oder 6, zur Herstellung von Clindamycinhydrochlorid.Hydrat, worin die Ausgangsverbindung Lincomycinhydrochlorid.Hydrat ist.

## Revendications pour les Etats Contractants: BE CH DE FR GB IT LI LU NL SE

1. Procédé de préparation de 7-halogéno-désoxylincomycine ou d'un de ses analogues, qui consiste (a) à faire réagir un composé de départ choisi entre la lincomycine et un de ses analogues, avec un halogénure d'amide répondant à la formule



dans laquelle chaque groupe Hal représente le brome ou le chlore, et R<sub>1</sub> et R<sub>2</sub> sont choisis indépendamment entre un groupe aryle et un groupe alkyle en C<sub>1-8</sub>, ou bien NR<sub>1</sub>R<sub>2</sub> représente un groupe morpholino ou un noyau hétérocyclique contenant dans le cycle 4 à 8 atomes choisis entre le carbone et l'azote, pour former un produit d'addition;

(b) à chauffer le produit d'addition pour former un 7-halogéno-7-désoxy-(produit d'addition); et

(c) à hydrolyser le 7-halogéno-7-désoxy(produit d'addition) avec une solution aqueuse de base.

2. Procédé suivant la revendication 1, dans lequel l'halogénure d'amide est un chlorure d'amide. 3. Procédé suivant la revendication 1, dans lequel le chlorure d'amide est choisi entre le chlorure de N-(chlorométhylène)-N-méthylméthanaminium, le chlorure de N-(chlorométhylène) pipéridinium, le chlorure de N-(chlorométhylène) morpholinium et le chlorure de N-(chlorométhylène) pyrrolidinium.

4. Procédé suivant l'une quelconque des revendications précédentes, destiné à la préparation de clindamycine, dans lequel le composé de départ est la lincomycine.

5. Procédé suivant la revendication 3, dans lequel le chlorure d'amide est le chlorure de N-(chlorométhylène)-N-méthylméthanaminium et le composé de départ est le chlorhydrate de lincomycine hydraté.

6. Procédé suivant la revendication 3, dans lequel le chlorure d'amide est le chlorure de N-(chlorométhylène) pipéridinium et le composé de départ est le chlorhydrate de lincomycine hydraté.

7. Procédé suivant la revendication 5 ou 6, destiné à la préparation d'hydrate de chlorhydrate de clindamycine, dans lequel le composé de départ est l'hydrate de chlorhydrate de lincomycine.

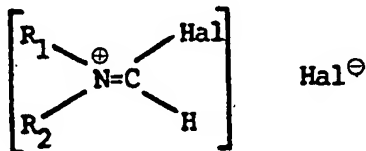
8. Produit d'addition de lincomycine ou d'un de ses analogues et d'un halogénure d'amide suivant l'une quelconque des revendications 1 à 3.

9. Produit d'addition de lincomycine et d'un halogénure d'amide suivant l'une quelconque des revendications 1 à 3.

10. Produit d'addition d'hydrate de chlorhydrate de lincomycine et d'un chlorure d'amide suivant la revendication 5 ou la revendication 6.

## Revendications pour l'Etat Contractant: AT

1. Procédé de préparation de 7-halogéno-7-désoxylincomycine ou d'un de ses analogues, qui consiste (a) à faire réagir un composé de départ choisi entre la lincomycine et un de ses analogues, avec un halogénure d'amide répondant à la formule



dans laquelle chaque groupe Hal représente le brome ou le chlore, et R<sub>1</sub> et R<sub>2</sub> sont choisis indépendamment entre un groupe aryle et un groupe alkyle en C<sub>1-8</sub>, ou bien NR<sub>1</sub>R<sub>2</sub> représente un groupe morpholino ou un noyau hétérocyclique contenant dans le cycle 4 à 8 atomes choisis entre le carbone et l'azote, pour former un produit d'addition;

(b) à chauffer le produit d'addition pour former un 7-halogéno-7-désoxy-(produit d'addition); et

(c) à hydrolyser le 7-halogéno-7-désoxy(produit d'addition) avec une solution aqueuse de base.

2. Procédé suivant la revendication 1, dans lequel l'halogénure d'amide est un chlorure d'amide.

3. Procédé suivant la revendication 1, dans lequel le chlorure d'amide est choisi entre le chlorure de N-

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(chlorométhylène)-N-méthylméthanaminium, le chlorure de N-(chlorométhylène) pipéridinium, le chlorure de N-(chlorométhylène) morpholinium et le chlorure de N-(chlorométhylène) pyrrolidinium.

4. Procédé suivant l'une quelconque des revendications précédentes, destiné à la préparation de clindamycine, dans lequel le composé de départ est la lincomycine.

5. Procédé suivant la revendication 3, dans lequel le chlorure d'amide est le chlorure de N-(chlorométhylène)-N-méthylméthanaminium et le composé de départ est le chlorhydrate de lincomycine hydraté.

6. Procédé suivant la revendication 3, dans lequel le chlorure d'amide est le chlorure de N-(chlorométhylène) pipéridinium et le composé de départ est le chlorhydrate de lincomycine hydraté.

7. Procédé suivant la revendication 5 ou 6, destiné à la préparation d'hydrate de chlorhydrate de clindamycine, dans lequel le composé de départ est l'hydrate de chlorhydrate de lincomycine.

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